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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BASKAR, PADMAVATHI

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	10/039, 170	Applicant(s)	WARD et al.
Examiner	Padmavathi v Baskar	Art Unit	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 15 April 2004.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-7, 9, 14, 15, 17, 20, 23-26, 30, 31, 34, 35, 38 and 39 is/are pending in the application.
- 4a) Of the above claim(s) 3-7, 9, 17, 20, 30, 31, 34 and 35 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-2, 14-15, 23-26, 38 and 39 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received. *XFB*

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Attachment(s)

- 1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2/25/02
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____

Response to Amendment

Response

1. Applicant's response to First Action On Merits filed on 4/15/04 is acknowledged.

Applicant states that the amendment to the claims is reflected in the listing of claims that begins on page 3. However, no such amendment to the claims has been found in the response filed on 4/15/04.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.
3. The examiner acknowledges the amendment made to the specification.

Status of claims

4. Claims 1-7, 9, 14-15, 17, 20, 23-26, 30, 31, 34-35 and 38-39 are pending in the application.

Claims 1-2, 14-15, 23-26, 38 and 39 are under examination.

Claims 3-7, 9, 17, 20, 30, 31 and 34-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected group.

Priority

5. In view of clarification of record and submission of the sequence that was submitted in the provisional application 60/247,870, priority is accorded as of the filing date of priority document 11/9/2000 for claims 1-2, 14-15, 23-26, 38 and 39,
SEQ.ID.NO: 1

Information Disclosure Statement

6. Applicant requests the examiner to sign the A2 reference and provide a signed copy of the same. The signed IDS (2/25/02) is attached here with the office action.

35 U.S.C. 112 written description rejection maintained

7. The rejection of claims 1-2, 14-15, 23-26 and 38-39 under 35 U.S.C. 112, first paragraph Written description rejection is maintained as set forth in the previous office action.

Claims are directed an isolated polypeptide comprising an antigenic fragment of SEQ.ID.NO: 1, fusion protein comprising said fragments, vaccine composition comprising said fragment or functionally active variant, said vaccine is a proteosome vaccine for *T.gondii*.

The instant specification teaches nucleic acid TgAMA1 sequence, SEQ ID NO: 2 and the polypeptide SEQ ID NO: 2, encoded by said nucleic acid from *Toxoplasma gondii*. The specification also teaches that this protein is similar to *P.falciparum* apical membrane protein (AMA) and involves in parasite invasion into the cell. However, there is no disclosure of antigenic fragment of SEQ.ID.NO: 1, fusion protein comprising said fragments, vaccine composition comprising said fragment or functionally active variant, said vaccine is a proteosome vaccine for *T.gondii*. Further, the instant specification teaches no potential vaccine composition comprising said TgAMA1 polypeptide or its antigenic fragments or functionally active variant, No specific fragments were described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While, one of skill in the art, may be able to experiment on a wide range of fragments in order to determine which fragment can inhibit the infection, without sufficient description as to where to begin with or which fragment would be an effective vaccine, the specification does not describe by any identifying characteristics or properties of fragments of *T.gondii* parasite protein. Therefore, the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective filing date**. These fragments do not meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at 1116.).

The actual structure or other relevant identifying characteristics of each fragment having the claimed properties of the polypeptide, SEQ.ID.NO: 1 can only be determined empirically by actually making every amino acid which can result in fragments which can identify the full length protein.

There must be some nexus between the structure of the polypeptide fragments and the function of that fragment. The specification fails to teach the structure or relevant identifying characteristics of fragments, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. With the exception of an isolated polypeptide comprising the amino acid sequence SEQ ID NO: 1,

fragments, fusion protein having said fragments or vaccine composition comprising said are not adequately described. Written description requires more than a mere statement that it is part of the invention and reference to a potential method for making it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad.

Applicant's arguments filed on 4/15/04 have been fully considered but they are not deemed to be persuasive.

Applicant states that the specification on pages 24 and 29 discloses antigenic fragments of SEQ.ID.NO: 1 and instant application fully discloses the SEQ.ID.NO: 1. Applicant keeps on pointing to the examiner where antigenic fragments and vaccine composition comprising said fragments have support and those of ordinary skill in the art knows transmembrane and extracellular domains of TgAMA-1.

The examiner disagrees with the applicant because the specification does not disclose an isolated TgAMA-1 comprising antigenic fragment of the polypeptide sequence as set forth in SEQ.ID.NO: 1. The specification teaches an isolated polypeptide consisting of antigenic fragment of SEQ.ID.NO: 1.

The examiner would like to point to the applicant that fragments as claimed are not shorter than SEQ.ID.NO: 1 because applicant is claiming an isolated polypeptide comprising (open language) antigenic fragment of SEQ.ID.NO: 1 and thus claiming an isolated polypeptide comprising any two amino acids from SEQ.ID.NO: 1 plus unlimited and unknown amino acids as fragments without any function. Thus, the fragments as claimed are broader than the claimed SEQ.ID.NO: 1. Please note applicant is not claiming an isolated polypeptide consisting of antigenic fragment as set forth in SEQ.ID.NO: 1.

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35 U.S.C. 112 scope of enablement rejection maintained

8. The rejection of claims 1-2, 14-15, 23-26 and 38-39 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide consisting of antigenic fragment of the amino acid sequence SEQ.ID.NO: 1 the specification does not reasonably provide enablement for any isolated polypeptide comprising an antigenic fragment of SEQ.ID.NO: 1, fusion protein comprising said fragments, vaccine composition comprising said fragment or functionally active variant, said vaccine is a proteosome vaccine for *T.gondii*. is maintained as set forth in the previous office action.

The specification describes the polypeptide SEQ ID NO: 1 that is encoded by a polynucleotide sequence, SEQ.ID.NO: 2 from *T.gondii*. The specification fails to indicate the biological activity of said fragments of SEQ ID NO: 1, fails to teach that SEQ ID NO: 1, a polypeptide that is detected by immune or convalescent sera and further lacks any description of polypeptide SEQ ID NO: 1 which acts as a vaccine. The specification is not enabled for fragments because 1) the specification fails to teach that the alleged polypeptide fragments of SEQ ID NO: 1 is able to function as a vaccine composition 2) the specification fails to teach how to make and use fragments thereof that have an unknown and uncharacterized function; 3) the specification fails to teach what are the critical residues that can be modified and still achieve a fragment with any functional activity or any fragments with vaccine characteristics for *T.gondii*. ; 4) the art teaches that polypeptides with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of the function of the polypeptide of SEQ ID NO: 1 as a vaccine and 5) applicants have not displayed a nexus between the structure of the fragments of SEQ.ID.NO: 1 and function of the polypeptide as a vaccine.

As to points 1)- 5), the specification fails to provide a written description of any fragments. The specification fails to teach the critical polypeptide residues involved in the function of the polypeptide SEQ ID NO: 1, such that the skilled artisan is provided no guidance to test, screen or make fragments of the polypeptide or the functionally active fragments of SEQ ID NO: 1 using conventional technology which allow for a vaccine use in the specification. The specification fails to teach to what extent one could alter SEQ ID NO: 1 and still present the sequence as a vaccine. Even if one were to use the in vivo vaccine methodology of the specification to screen for a vaccine, one of skill in the art would be reduced to merely randomly altering amino acid(s), which would lead to unpredictable results regarding the functional activity of the polypeptide to be used as a vaccine. Moreover, polypeptide chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in

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"PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a polypeptide leads to unpredictable changes in the biological activity of the polypeptide. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the polypeptide (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a polypeptide. Polypeptides with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products polypeptides that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition.

Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient to provide for enablement of vaccines. This specification fails to teach any immune response generated by means of a nucleic acid -vaccine. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach even one of the claimed polynucleotide encoding polypeptides or fragments thereof alone or in combination with other antigens does in fact confer protection from infection, as is requisite of a vaccine composition. The specification fails to teach that the claimed polynucleotide encoding a polypeptide peptide or fragment or variant thereof are able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize other similar nucleic acids as operative vaccines.

The state of the prior art indicates that little is known about the AMA protein and it's as a vaccine composition. Hehl et al teaches antiserum to TgAMA1 blocked invasion of host cell only by approximately 40% in *invitro* experiments. However, whether this protein blocks the parasite invasion in animal model is yet to be experimented. At present, the invasion of host cells by asexual stages of apicomplexan parasites is a complex process and receptor-mediated event is still not well understood (Hehl et al, Infection and Immunity, December 2000, p. 7078-7086, Vol. 68, No. 12). Therefore, the claimed protein induces an effective immune response such that it can block the invasion of parasites completely and it can be used, as a vaccine composition is not predictable in this underdeveloped art. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for any *in vivo* uses of the claimed protein.

In the absence of a teaching of the claimed polypeptide can generate an immune response and that immune response is effective in prevention of disease, the

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specification is not enabled for vaccines. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

Please note that there is a typographical in not including the claims 23-26 in previous office action. The examiner regrets any inconvenience caused by this.

Applicant's arguments filed on 4/15/04 have been fully considered but they are not deemed to be persuasive.

Applicant states (pages 11-15 of the response) that the specification on pages 6, 8, 19, 24, 29 disclose antigenic fragments of SEQ.ID.NO: 1 and instant application is fully discloses the SEQ.ID.NO: 1 and keeps on pointing to the examiner various pages of the specification for support of antigenic fragments, variant and vaccine composition comprising said fragments.

The examiner disagrees with the applicant because the specification does not disclose an isolated TgAMA-1 comprising antigenic fragment of the polypeptide sequence as set forth in SEQ.ID.NO: 1. The specification teaches an isolated polypeptide consisting of antigenic fragment of SEQ.ID.NO: 1.

The examiner would like to point to the applicant that fragments as claimed are not shorter than SEQ.ID.NO: 1 because applicant is claiming isolated polypeptide comprising (open language) antigenic fragment of SEQ.ID.NO: 1 and thus claiming an isolated polypeptide comprising a fragment from SEQ.ID.NOs: 1 plus unlimited and unknown amino acids as antigenic fragments without any function. Thus, the fragments as claimed are broader than the claimed SEQ.ID.NO: Please note applicant is not claiming an isolated polypeptide consisting of antigenic fragment as set forth in SEQ.ID.NO: 1. The examine regrets the error made on page 8 of the previous office action in reciting "nucleic acid encoding polypeptide" and it should have been polypeptide fragments.

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Applicant states that the level of skill in the art has an important effect on the amount of guidance, which must be provided to enable the invention. Thus the level of knowledge of one of ordinary skill in the art cannot be ignored in the Wands factor analysis.

The examiner has clearly analyzed the factors and made the rejection by considering the level of knowledge of one of ordinary skill in the art. As explained above, one of ordinary skill in the art readily recognizes an isolated polypeptide consisting of antigenic fragment as set forth in SEQ.ID.NO: 1 but not an isolated polypeptide comprising (open language) antigenic fragment of SEQ.ID.NO: 1 because the transitional limitation "comprises" similar to the limitations, such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Molecular Research Corp. v. CBS, Inc.*, 793 F2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open. for the inclusion of unspecified ingredients even in major amounts". On the other hand, the limitation "consisting of represents closed claim language and excludes any element, step, or ingredient not specified in the claim. In *re Gray*, 53 F. 2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948).

Claim Rejection - 35 USC 102 maintained

9. The rejections of claim 1 under 35 U.S.C. 102 (b) as being anticipated by Hehl et al 1997, Accession number: AF010264 and Hehl et al Accession number: O15681, 1998 are maintained as set forth in the previous office action.

The claim is drawn to an isolated polypeptide comprising an antigenic fragment of SEQ.ID.NO: 1.

Hehl et al disclosed an isolated polynucleotide encoding T.gondii apical membrane antigen (AMA1 Tg) comprising the 541 amino acid sequence (see the attached accession number). The disclosed protein is 100% identical with the claimed protein, SEQ.ID.NO: 1. Therefore, the prior art anticipated the claimed invention.

Accession number: O 15681, 1998, disclosed the apical membrane antigen comprising 541 amino acids. The disclosed protein is 100% identical with the claimed

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protein, SEQ.ID.NO: 1. Therefore, the prior art anticipated the claimed invention is maintained as set forth in the previous office action.

Applicant's arguments filed on 4/15/04 have been fully considered but they are not deemed to be persuasive.

Applicant states that the applicant is claiming an antigenic fragment of SEQ.ID.NO: 1 and not the full length. Therefore, the rejection should be withdrawn.

The examiner disagrees with the applicant because an isolated polypeptide comprising an antigenic fragments of SEQ.ID.NO: 1 is considered broader than SEQ.ID.NO: 1 because an isolated polypeptide comprising the amino acid is a species over the presently claimed an isolated polypeptide comprising an antigenic fragment of SEQ.ID.NO: 1 is broader and considered as a genus of said species. Therefore, this rejection is maintained.

10. In view of the priority accorded to this application, the rejection of claims 1-2 and 23-26 under 35 U.S.C. 102 (a) as being anticipated by Hehl et al 2000, Infection and Immunity, December 2000, p. 7078-7086, Vol. 68, No. 12 is withdrawn.

11. In view of submission of the Declaration under 37CFR 1.132 of record, the rejection of claims 1 and 23-25 under 35 U.S.C. 102 (a) as being anticipated by Donahue et al 2000, Molecular Parasitology Meeting, Woods Hole, MA poster Sep, 17 – 21 is withdrawn.

Remarks

12. No claims are allowed.

Conclusion

13. This application contains claims 3-7, 9, 17, 20, 30, 31 and 34-35 that are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a

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nonelected inventions. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

15. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.
